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# Alternative and Complementary Approaches to Treating Common Ocular Disorders

## *Part 2—Retinopathy and Macular Degeneration*

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*In Part 1 of this article (see ALTERNATIVE & COMPLEMENTARY THERAPIES 8:17–22, 2002), natural therapeutic approaches for treating cataracts and glaucoma were reviewed. We concluded that it is best, first and foremost, to protect complex ocular structures against damage, using natural methods and that provision of treatment is necessary when protection fails. Part 2 covers diabetic retinopathy and age-related macular degeneration.*

A review of the literature showed that alternative approaches are frequently safe and effective for treating various eye conditions. Part 2 of this article completes our look at alternative medical approaches to common ocular diseases. It is worth noting that disturbances of the biochemistry of the eye leading to the pathophysiologic manifestations of disease are rarely limited to the eye but rather “as the eye goes so does the body.”

### **Diabetic Retinopathy: Description and Etiology**

Several conditions can cause damage to the retina of the eye, with long-term uncontrolled diabetes mellitus and poorly managed hypertension being the two most frequent problems. This article covers, specifically, diabetic retinopathy (DR).

DR is an ocular abnormality that is associated with poorly controlled diabetes and is defined by the presence of microaneurysms, punctate hemorrhages,

white and yellow exudates, flame hemorrhages, and neovascular vessel growth.<sup>1</sup> DR is the leading cause of blindness in patients with type 1 diabetes. The degree of retinal damage is closely associated with the length (generally not less than 10 years) of the disease process and the degree of glucose regulation and monitoring.

There are numerous mechanisms that have been proposed to explain the development of retinal changes in diabetes. One of the causes of diabetic retinopathy is the development of glycosylated proteins (the attachment of sugars to proteins in the presence of high blood glucose).<sup>2</sup> Glycosylated proteins lead to the development of oxidative free radicals, resulting in tissue damage and glutathione depletion. Studies on laboratory-induced diabetes in dogs and rats have shown a deficiency of glutathione in the retinas.<sup>3</sup> Human patients with diabetes who have retinopathy have higher levels of an oxidative stress byproduct called malondialdehyde compared to patients with diabetes who do not have retinopathy and who have healthy sugar controls.<sup>4</sup> Glycosylated proteins can be combined with lipids and become influenced and altered by free radicals; this leads to the formation of advanced glycated endproducts (AGEs), which can be deposited in blood vessels of the retina and contribute to neovascularization. Alternative and complementary medicine (ACM) research has been oriented toward the use of antioxidants to alter the free-radical pathway and to reduce retinal damage.<sup>5</sup>

It is no wonder that the sentinel treatment for DR is closely controlling blood sugar levels. The Diabetes Control and

Complications Trial studied 1439 patients with diabetes who used insulin and who had retinopathy. The effect of standard insulin dosing (two daily injections) was compared to tighter control with frequent glucose testing and injections throughout the day. During the first few months of the study, tighter blood-sugar control appeared to worsen retinopathy more than the conventional approach; however, better glucose monitoring resulted in a significant decrease in long-term risk.

### **Prevention and Treatment of DR**

Preliminary evidence points to the influence of free-radical formation and the development and progression of many forms of retinopathy.<sup>6</sup> Antioxidant formulas have long been the front-line defense in preventing and managing retinopathy. With properties that include free-radical scavenging, preventing protein glycosylation, and decreasing capillary permeability and fragility, it is no wonder that vitamin C is chief among these therapies.<sup>7–10</sup> Vitamin E, also a potent intracellular antioxidant, is considered to be effective, at a level of 1200 international units (IU) per day or more, for preventing and treating similar conditions.<sup>11</sup> Vitamins C and E have been shown, in limited investigations, to be present in lower levels in patients with diabetes compared to healthy controls.<sup>12,13</sup> In addition, vitamin E has been shown to protect people with very high cholesterol levels from developing retinopathy.<sup>14</sup> A combination of 500 mcg of selenium, 800 IU of vitamin E, 10,000 IU of vitamin A, and 1000 mg of vitamin C, taken each day for several years, has reduced diabetic retinopathy in a single research study.<sup>15</sup> Additional

## Study data indicated that patients who took a vitamin B<sub>6</sub> supplement seemed to have an absence of retinal involvement.

research has yielded similar benefits from the administration of  $\alpha$ -lipoic acid, a powerful inhibitor of oxidative glycosylated proteins.<sup>16</sup>

Researchers have found an increase in activity of the enzymatic diacylglycerol protein kinase C (DAG-PKC) pathway in the retinas of animals with diabetes.<sup>17</sup>

This increased enzyme activity appears to interfere with normal circulation to the retina. Vitamin E has been found to normalize the activity of the DAG-PKC pathway, which leads to improved retinal blood flow. Research has shown an additional possible mechanism for improved retinal blood flow via supplementation with vitamin E because of its influence on decreasing platelet aggregation.<sup>18</sup>

Low blood levels of magnesium, a nutrient that is vital to vascular health and integrity, have been linked to DR.<sup>19,20</sup> In a study of 71 people with insulin-dependent diabetes, subjects were divided into two groups, depending on the severity of their DR. All subjects had some degree of magnesium deficiency. The subjects with the most severe DR had the most significant deficiency of the mineral.<sup>20</sup> However, using magnesium supplementation to treat DR, has not been fully studied. Thus, while the results of this study are interesting and addressing a deficiency of the mineral is desirable, it is not prudent to treat DR with this supplement.

In a preliminary analysis, a group of researchers proposed that vitamin B<sub>6</sub> supplementation could be used to prevent diabetic retinopathy.<sup>21</sup> The researchers studied data gathered over a period ranging from 8 months to 28 years. The data indicated that patients who took a vitamin B<sub>6</sub> supplement seemed to have an absence of retinal involvement.

Bioflavonoids, such as quercetin, hesperidin, and naringin, are known to be involved in sorbitol metabolism and the additional development of oxygen free-

### Therapeutics for Eye Conditions

1. *Vitamin C*—At least 500–1000 mg per day often recommended; however, much greater dosages are not uncommon
2. *Vitamin E*—400–800 international units (IU) per day for adults
3. *Vitamin A*—10,000 IU, in divided doses, per day; for males and postmenopausal women, up to 25,000 IU (7500 mcg) of vitamin A per day considered safe; for women who could become pregnant, the safest intake level is being reevaluated; less than 10,000 IU (3000 mcg) per day widely accepted as safe
4. *Beta-carotene*—Most common beta-carotene supplement intake is probably 25,000 IU (15 mg) per day, although some people take as much as 100,000 IU (60 mg) per day
5. *Lutein*—6 mg (with food to decrease gastric upset) per day for adults
6. *Quercetin*—400 mg 3–4 times per day
7. *Coenzyme Q10*—20–150 mg per day, in divided doses
8. *Selenium*—100–200 mcg per day for adults
9. *Rutin*—400–1000 mg per day
10.  *$\alpha$ -Lipoic acid*—150–900 mg per day, recommended for general antioxidant protection
11. *Magnesium*—250–350 mg per day for adults
12. *Bioflavonoids*—1000 mg of citrus bioflavonoids or 400 mg of quercetin, each 3 times per day
13. *Ginkgo*—120–160 mg of *Ginkgo biloba* extract, standardized to contain 6 percent terpene lactones and 24 percent flavone glycosides, 2–3 times per day
14. *Bilberry*—In capsules or tablets standardized to provide 25 percent anthocyanosides, 240–480 mg per day
15. *Coleus*—2-percent *Coleus forskoliin* solutions applied topically
16. *Melatonin*—200 mcg; however, doses from 1 to 3 mg, 2–3 hours before bedtime have shown efficacy

### Quick Reference to Therapeutics for Diabetic Retinopathy and Age-Related Macular Degeneration

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Diabetic retinopathy	X	X	X	X		X	X				X					X
Age-related macular degeneration	X	X	X	X	X	X		X					X	X		

## Many natural-medicine doctors prescribe 400 mg of quercetin three times per day for patients with diabetes.

radicals. Thus, when treating patients with diabetes, these bioflavonoids should be considered as a means of inhibiting the enzyme aldose reductase.<sup>22</sup> Although human studies have not been done using quercetin to treat retinopathy, many natural-medicine doctors prescribe 400 mg of quercetin three times per day for patients with diabetes.

Botanical medications that have been helpful for treating DR include:

- *Vaccinium myrtillus* (bilberry), standardized to contain 25 percent anthocyanosides (a flavonoid that stabilizes connective tissues<sup>23</sup> and decreases capillary fragility<sup>24</sup>), produces powerful antioxidant effects and appears to have a particular affinity for the retina. Such an extract, when taken in doses between 80 and 160 mg, three times per day, has benefited patients with DR.<sup>25</sup>
- A standardized extract of *Ginkgo biloba* (ginkgo) has been shown to improve impaired color vision in people with DR.<sup>26</sup> The extract was standardized to 24 percent glycosides. In animal experimentation, ginkgo had significantly greater efficacy for reducing DR after 2 months compared to animals who were given placebo. The effect was attributed to this herb's antioxidant effects.<sup>27</sup> Most often, 60 mg of an extract is taken 2–4 times per day.

Improving blood flow, normalizing blood-sugar levels, and correcting for underlying metabolic disturbances appears to be the main therapy for retinal pathology. Considerable evidence

### Quick Reference to common Signs and Symptoms of Diabetic Retinopathy and Age-Related Macular Degeneration

	BV	VL	HV	EP	M	S	RR
Diabetic retinopathy	X	X					
Age-related macular degeneration	X	X				X	

BV = blurred vision; VL= vision loss; HV= halo vision; EP = eye pain; M = mydriasis; S = scotoma; RR = absent red reflex.

points to the benefits of potent antioxidant supplements. Vitamin E is the major choice at this time. However, like many other popular ACM modalities, extensive prospective clinical studies have not been conducted. The future seems bright indeed for patients with DR as more research emphasis is pushed toward ACM studies on treating this condition.

#### Macular Degeneration: Description and Etiology

Macular degeneration (MD), a group of diseases associated with loss of the central vision portion of ocular activity, is marked by damage to the pigment and neural and vascular layers of the macula. MD is the main cause of blindness in the United States and accounts for blindness in approximately 80 percent of people who are 75 or older.<sup>17</sup>

Macular degeneration, also called age-related macular degeneration (ARMD), is a painless, degenerative eye disease. Because the macula is the primary site affected by this condition, central visual acuity is affected while peripheral vision

may be completely spared. There are two forms of ARMD: (1) Nonexudative or dry ARMD involves the accumulation of drusen (debris deposits) between the pigment epithelium and the underlying basement membrane (Bruch's membrane). (2) The exudative or wet form involves neovascularization in response to the degenerative changes.<sup>28</sup>

ARMD is the leading cause of legal blindness in the United States in persons over 55. This condition affects more than 10 million Americans and this number will increase as the "baby boomers" age.

Although the etiology of macular degeneration is not fully understood, evidence from animal studies indicates free-radical damage from light exposure as a potential contributing factor.<sup>29</sup> The photoreceptors of the eye are high in polyunsaturated fatty acids, particularly docosahexaenoic acid (DHA). DHA is readily oxidized in the oxygen-rich environment of the retina.<sup>29,30</sup> Several of the known risk factors for ARMD, including cigarette smoking and sunlight exposure, appear to be at least partially related to oxidative stress.

## Bilberry has also been shown to strengthen capillaries and reduce hemorrhaging in the retina.

### Prevention and Treatment of ARMD

Sunlight triggers oxidative damage in the eye that, in turn, can cause ARMD.<sup>31</sup> Animals who were given antioxidants, which protect tissues against oxidative damage, have had a lower risk of developing this vision problem.<sup>32</sup> People with high blood levels of antioxidants also have a lower risk.<sup>33</sup> Those with the highest levels of the antioxidants selenium, vitamin C, and vitamin E may have a 70-percent lower risk of developing ARMD.<sup>34</sup> People who eat diets that are rich in beta-carotene, another antioxidant, also appear to be at a lower risk for developing ARMD.<sup>35</sup> As such, many people who want to lower their risk for macular degeneration take antioxidants. Reasonable adult levels include 200 mcg of selenium, 1000 mg of vitamin C, 400 IU of vitamin E, and 25,000 IU of natural beta-carotene per day.

The carotenoids lutein and zeaxanthin are antioxidants much like beta-carotene. These carotenoids, which are found in high concentrations in spinach and kale, concentrate in the part of the retina where ARMD strikes. The macula acquires its yellow appearance from the accumulation of carotenoid pigments. Lutein is found in higher concentrations outside of the fovea while zeaxanthin concentrates closer to the fovea.<sup>35</sup>

Research has shown that carotenoids act to protect the retina from damage caused by sunlight.<sup>36</sup> People who eat spinach and kale have a lower risk of developing ARMD, although blood levels of lutein have not been correlated with a risk of macular degeneration.<sup>37</sup>

Two important enzymes needed for vision in the retina require zinc (an outstanding ally in free-radical defense). Double-blinded research, using 80 mg of zinc versus placebo for 2 years, found that zinc prevented 42 percent of vision loss in subjects with ARMD.<sup>38</sup> Additional research did not, however, confirm the data generated from this earlier study.<sup>39</sup>

Active bioflavonoid compounds (anthocyanosides) in bilberry act as antioxidants in the retina. This makes the herb a potential preventive measure against macular degeneration.<sup>40</sup> Bilberry has also been shown to strengthen capillaries and reduce hemorrhaging in the retina.<sup>41</sup> Many people take 240–480 mg per day of bilberry extract in capsules or tablets standardized to 25 percent anthocyanosides. Additional research has shown promise for the antioxidant effects of ginkgo for preventing or treating macular disorders.<sup>42</sup>

Promising preliminary research points toward the profound effect that vitamin and nutrient antioxidants have on macular function. Once again, the future of therapies relies strongly on preventive medical measures. Counseling patients regarding reducing exposure to oxidative damaging environments and activities, increasing antioxidant-rich food sources, and increasing activities that influence blood flow to the eye, will be the most potent therapeutics. However, in circumstances when treatment is needed, sound scientific support is becoming available to justify treatment with nutrients and botanicals including carotenoids, vitamins C and E, zinc, selenium, and ginkgo. □

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